John G. Curtis

Compliments of D. R. Lucas.

PHYSIOLOGICAL AND PHARMACOLOGICAL STUDIES OF THE URETER. III.

— BY —

DANIEL R. LUCAS, M.A., M.D.

DISSERTATION
Submitted in partial fulfilment of the requirements for the Degree of Doctor of Philosophy, in the Faculty of Pure Science, Columbia University.

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By DANIEL R. LUCAS.

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CONTENTS.

		Page
I.	On transmission of pressure from the bladder to the kidney	245
II.	Ureteral pressure	250
III.	Ureteral pressure and renal circulation	259
IV.	Ureteral pressure and the flow of urine	263
V.	Biochemical influences on ureteral pressure	266
VI.	Summary of general conclusions	277

I. On Transmission of Pressure from the Bladder to the Kidney.

Introductory. — It is often said that "distention of the bladder seems to cause congestion of the kidneys and, when frequent and long continued, may even be etiological of nephritis." At various times clinicians have asked whether I have noticed regurgitation of urine into the ureter from the bladder.

Although I have been unable to find any exception to the statement that the so-called uretero-vesicular valve is normally quite competent, such questions as the one mentioned above indicate the existence of some doubt as to whether pressure in the bladder may have an effect on the kidneys by direct transmission through the ureter, or only by indirect nervous influence. Publication of some of my notes regarding this matter may therefore be of interest.

Experimental. — My first observation in this connection was made during an investigation of normal ureteral pressure and its relation to the peristaltic movements of the ureter in the dog.[2]

[1] The first paper was published in this journal, 1906, xvii, p. 392; the second paper appeared in the New York medical journal, 1907 (August 10).

[2] Lucas: Proceedings of the Society for Experimental Biology and Medicine, 1905, ii, p. 61; also Science, 1905, xxi, p. 721; American medicine, 1905, ix, p. 744; Medical news, 1905, lxxxvii, p. 87.

In that series of experiments a cannula, maintained without ligatures and not materially interfering with either the flow of urine or the peristalsis of the ureter, was inserted in the ureter at various locations between the kidney and the bladder. It was connected with a water manometer, fitted with float and style to record, on a revolving smoked drum, the intra-ureteral pressure and the effect of the peristaltic waves on that pressure. It was noted that if a kink in, or compression of the ureter below the cannula prevented flow from the ureter, a proportionate increase was registered in the amount of intra-ureteral pressure and the number of peristaltic contractions, — results that confirmed the related conclusions of Sokoloff and Luchsinger.[3]

An unsuccessful attempt was made to cause a more rapid rise in intra-ureteral pressure than was obtainable by the collection above the clamp of urine secreted by the kidney, by squeezing the well-filled bladder with the hand. This was done in a number of animals and frequently repeated in the same animal. In all but one case it was found to be *impossible* to cause in this way increased intra-ureteral pressure. In the one exceptional case the left uretero-vesicular valve seemed to be deficient. The right valve, however, was entirely competent. The force exerted on the bladder in these experiments was sufficient in each case to overcome the compressor-urethra muscle and empty the bladder, or, when the urethra was clamped, to burst the bladder. In the ureter *in situ*, the animal being narcotized with morphine, the rate of ureteral peristalsis recorded on a smoked drum was, as a rule, increased by the manipulation. This increased contraction was apparently caused by nervous influence and not by mechanical distention (Protocol No. 1).

The competency of the uretero-vesicular valve was noted in five different experiments in which, also, the ureteral pressure was observed as described in Protocol No. 1. The nozzle of a ten-ounce metallic syringe was firmly ligated into the bladder or urethra, and salt solution injected until the bladder burst, without affecting the ureter pressure in any instance (Protocol No. 2). In five perfusion experiments the recording apparatus was not attached, the ureter being merely inspected and palpated. Pressure exerted as described in Protocol No. 2 did not cause dilatation of the ureter. In all

[3] Sokoloff and Luchsinger: Archiv für die gesammte Physiologie, 1881, xxvi, p. 464.

these experiments the freedom of flow of the perfusion fluid through the kidney vessels was never retarded in the slightest degree by pressure exerted in the bladder (Protocol No. 3). When pressures of 20 to 40 cm. of water were produced in the ureter by injection of Ringer solution through a cannula inserted above the uretero-vesicular valve, the venous flow from the kidney was markedly diminished and the distention of the ureter could be plainly seen and palpated (see Fig. 1).

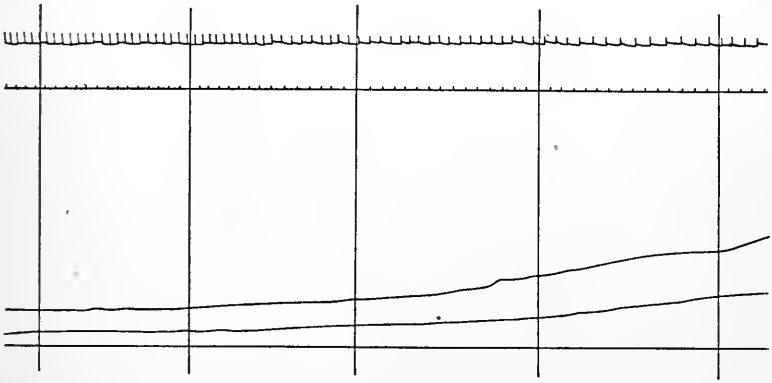

FIGURE 1. Upper tracing, drops of fluid from cannula in renal vein. Second tracing from top, time marked in seconds. Third tracing from top, from *L* cannula in middle portion of the ureter. Fourth tracing from top, pressure in renal pelvis registered through a trocar cannula. Straight line, base line for both pressure curves.

A series of experiments were performed by Dr. Burton-Opitz and myself, in the Physiological Laboratory of the College of Physicians and Surgeons, on the circulation of the blood in the kidneys of dogs anesthetized with ether. We investigated the effect of various pressures exerted at different places in the ureter, and in the bladder, on the rate of blood flow through the kidney, as measured with the Burton-Opitz stromuhr. It was found that the amount of pressure necessary to almost absolutely suppress the flow through the kidney when exerted in the ureter varied directly with the nearness of insertion of the cannula to the pelvis of the kidney. That variation of pressure ranged between 10 to 50 mm. of mercury.[4]

We were unable to note any change in the rate of flow of blood through the kidney in the experiments in which we recorded the

[4] BURTON-OPITZ and LUCAS: Proceedings of the Society for Experimental Biology and Medicine, 1908, v, p. 44.

flow from one kidney while special pressure was exerted in the opposite ureter. The results obtained by pressure in the bladder, which was accomplished by compressed air injected at different constant pressures through the urethra, and tried in increasing degrees up to one sufficient to burst the bladder, were also negative.

In these experiments the animals had previously been subjected to various other tests: to prolonged anesthesia with ether and chloroform; their abdominal contents had been exposed and manipulated; and often the renal nerves isolated and stimulated by electricity. Consequently a reflex nerve connection between bladder and kidney or between the two kidneys might easily have been interfered with or destroyed.

In all experiments in which the flow of blood through a kidney was reduced by pressure in its ureter, the blood flow rapidly returned to normal when the pressure was released.

When the bladder was removed from an animal and water injected into it through the urethra until it burst, no leakage was, as a rule, produced through the ureters.

Conclusions. — The results of these precise experiments accord with the experience of many a boy who has observed that a pig's bladder can be inflated with air by means of a quill inserted in the urethral opening; that such inflation can be made permanent by ligation of the urethra, no attention to the ureters being required; and that the bladder thus distended can be used as a football for days. This shows without doubt that the normal uretero-vesicular valves are entirely competent, and that they wholly prevent the slightest reflux of urine under any degree of pressure which can obtain in the bladder.

Therefore, as has been suggested above, if a continuous or frequently distended bladder has a deleterious effect on the kidney, this effect must be brought about, not by any direct transmission of pressure from the bladder to the kidney, but entirely by a nervous mechanism.

The latter will be considered more fully in a later research.

Protocols. I. Dog; weight, 24.56 kilos. Milk diet for twenty-four hours before the beginning of the experiment. Morphine (6 mg. per kilo) was injected hypodermically at 9.45 A. M., June 23, 1906. 11 A. M. Animal profoundly narcotized. A trocar cannula was introduced through the cortex and medulla of the kidney so

that it just entered the renal pelvis. The cannula was retained in place by a purse-string suture around the point of puncture of the capsule of the kidney. The urine aspirated fresh from the bladder was injected through the cannula, and the patency of the cannula and the ureter ascertained. An improved T cannula was inserted in the lower third of the ureter. Each cannula was connected with a water manometer and the pressure changes were recorded by means of an Emerson float,[5] on the smoked drum of a kymograph. At first a slightly positive pressure was recorded from the cannula in the straight portion of the ureter, and also from the cannula in the pelvis of the kidney. After a saline infusion of about 400 c.c. in the femoral vein, the amount of secreted urine and the rate of peristalsis were increased, but the intra-ureteral *pressure was decreased.* The bladder, which was distended with urine, was grasped by the hand, and pressure gradually exerted until the sphincter was overcome and the urine released. This had no effect on the pressure recorded by either manometer, but the irritation of the bladder called forth an increased peristalsis. After the urine had escaped, the pressure recorded by the cannulas remained about the same as previously. However, the variations in pressure caused by each peristaltic contraction were not so great for a time as they had been, but subsequently the waves resumed the original size.

2. Bull dog; weight, 16.8 kilos. Morphine, 0.168 gram at 9.40 A. M., July 3, 1905. Several additional small doses of morphine between 10.40 and 11.20. Two cannulas in the ureter of the right kidney: one, a trocar cannula through the cortex and medulla of the kidney into the renal pelvis, the other an improved T cannula, were inserted at the junction of the upper and middle thirds of the ureter. A straight glass cannula was inserted in the left ureter for collecting and measuring the flow of urine.

As the animal seemed to exhibit special tolerance for morphine, a small amount of chloroform was administered from time to time. A positive pressure of 2 cm. of water was registered from the straight portion at times when the chloroform was used, which caused retardation of the muscular action of the ureter.[6] As the effect of the chloroform wore off, the pressure in the pelvis of the kidney increased, and the pressure in the straight portion of the ureter fluctuated about a neutral point. One gram of diuretin in 30 c.c. of physiological salt solution was infused in the femoral

[5] EMERSON: Proceedings of the Society for Experimental Biology and Medicine, 1904–1905, ii, p. 38.

[6] LUCAS: New York medical journal, August 10, 1907.

vein. It gave rise to a flow from the left kidney of 1 c.c. of urine in eight minutes. The tip of a ten-ounce hand syringe was inserted at the urethro-vesicular opening and securely ligated in place. The urethra was clamped, and salt solution was injected into the bladder until the bladder burst. No increase in the pressure in the ureter was shown by the manometer.

3. February 18, 1908. — The kidney, ureter, and bladder of a dog were collectively removed. The cannula and recording instruments were adjusted as described in Protocol No. 2. Ringer solution was perfused into the renal artery at a constant pressure of 100 cm. The fluid from the renal vein was collected in a graduated cylinder, and record was made of the time which elapsed while 200 c.c. were collected, with the following results:

Time.	Fluid from the vein. c.c.	Tests applied.
12.57 P.M.	0.0	....
1.11 P.M. (14 min.)	200.0	....
1.29 P.M. (18 min.)	200.0	The urethral outlet was clamped and the bladder was severely squeezed with the hand.
1.48 P.M. (19 min.)	200.0	....
2.09 P.M. (20 min.)	200.0	Ringer solution was injected into the bladder until it burst.
2.29 P.M. (20 min.)	200.0	....

NOTE. — The tendency of the vein flow gradually to decrease, as shown by the above figures, cannot be attributed in any degree to the manipulation of or pressure exerted in the bladder. It is a phenomenon observed during the first few hours of all kidney perfusion experiments, and has been accurately described and charted by Sollmann.[7]

II. Ureteral Pressure.

Introductory. — The so-called ureteral pressure, which has been the subject of many studies, is, as pointed out by Henderson,[8] a misnomer. In the investigations of the so-called ureteral pressure it was not the pressure exerted by the ureter that was studied, but the pressure of the kidney secretion as observed by a manometer tied in the ureter. Sokoloff and Luchsinger, Henderson, and others observed that the ureter is capable of contractions sufficiently strong to overcome a very considerable intra-ureteral pressure. They stated that within physiological limits the rate of contraction was directly

[7] SOLLMANN: This journal, 1905, xiii, p. 249.

[8] HENDERSON: Journal of physiology, 1905–1906, xxxiii, p. 175.

proportional to the pressure. I have seen contractions in an isolated piece of the middle portion of a ureter from a small dog lift a pressure column of Ringer solution 92 cm. high. I have also recorded graphically contractions under a pressure of 86 cm. of the same solution, which recurred as often as four to five times per minute and, without decreased frequency, for forty minutes, at the end of which time the pressure was diminished. Pharmacological experiments were satisfactorily conducted on this ureter for some time thereafter.

As I pointed out in a previous paper,[9] the ureteral peristalsis is composed not only of wave motions, due to the shortening of both longitudinal and circular fibres, that travel from kidney to bladder, as described by Engelmann, but also of wave motions in at least that portion of the ureter contained in the renal pelvis, which are distinct and different from the contractions of the straight portion. I believe that further research will justify the general division of the ureter into the following two portions which are distinctly unlike each other in the character of their contractions and functions.

1. The funnel-shaped portion above the isthmus contained in the renal pelvis and probably partaking of the nerve distribution to the kidney.

2. The straight portion extending from the isthmus to the bladder, which may be subdivided into (*a*) an upper third, containing nerve endings in its wall; (*b*) a middle third, deficient in nerve endings; and (*c*) a lower third, adjacent to the bladder and partaking to some extent of the nerve distribution to the bladder.

I have often found that the ureter is capable of forcing urine into the bladder, even when sufficient pressure is gradually exerted in the bladder to burst it, no rise of pressure taking place in the ureter either from regurgitation or accumulation of urine secreted by the kidney.

Various investigations of the so-called ureteral pressure have shown that pressures varying from 5 to 20 cm. of water cause variable effects on the amount and constituents of the urine. Thus Steyrer[10] found that pathological closure of one ureter caused an increased flow, diminished specific gravity, and lowered freezing-point of the urine. Pfaundler[11] observed an increased flow in three

[9] Lucas: This journal, 1906, xvii, p. 392.

[10] Steyrer: Beiträge zur chemischen Physiologie und Pathologie, 1902, ii, p. 312.

[11] Pfaundler: *Ibid.*, 1902, ii, p. 336.

dogs and in one woman under similar circumstances. Schwarz[12] noticed that pressures of 10–25 cm. of oil increased the flow of urine, but that greater pressure decreased the flow. Cushny[13] found, without exception, that a pressure of 19.5 cm. of water diminished urinary flow in rabbits. Sollmann[14] concluded from his experiments that the cause of the increase is due to forces vital and not mechanical.

The above-mentioned observations, in the light of my own experience with the ureter, lead me to raise this question: May not the living ureter antagonize transmission of pressure towards the kidney? I believe that definite conclusions on the effect upon the kidney of pressure exerted in the ureter, *in situ* or *überlebend*, are unwarranted before we know definitely how internal pressure influences the ureter. We should know not only the effect in the portion below the isthmus, but also in the portion in the renal pelvis, and the relation of the pressure in these two portions to each other, both normally and when artificially produced.

Before proceeding to a description and discussion of my experiments intended to answer this question, I wish to emphasize one point. In the above statement, *überlebend* (*i. e.*, surviving) is used advisedly. The maintenance for many hours of vital contractile activity in the ureter when excised has made it a very satisfactory subject for the study of many points regarding involuntary muscle tissue. Not long ago I published a tracing showing the effect of caffein on an excised ureter which had been kept in physiological salt solution for five hours after the animal had been killed by pithing.[15] Subsequently, in studies on the ureter and kidney which had been excised jointly and together placed in warm Ringer solution, contraction waves occurred with surprising rapidity and strength during perfusion of the kidneys with Ringer solution twenty-seven hours after their removal from the animal. These waves were graphically recorded. This observation, it will be noted, was made on the second day of the experiment. The temperature of the bath had been allowed to fall to that of the room before the end of the first day and the perfusion fluid had been withheld nineteen hours. Moreover, the peristalsis had been en-

[12] Schwarz: Centralblatt für Physiologie, 1902, xvi, p. 281.
[13] Cushny: Journal of physiology, 1902, xxviii, p. 431.
[14] Sollmann: This journal, 1905, xiii, p. 276.
[15] Lucas: New York medical journal, August 10, 1907.

tirely inhibited at the end of the first day's experiment by the use of barium chloride, my intention being to study on the second day the effect of pressure on the dead ureter and kidney as compared with that on the living ureter and kidney on the previous day. Such observations emphasize the vigorous and prolonged vital activity of the excised ureter, — a fact in harmony with similar qualities of the excised kidney, as has been pointed out by Sollmann.[16]

Experimental. Methods. — The present experiments were made on dogs only. As a rule large animals were selected. The ureter was connected with a recording apparatus by

(*A*) An improved cannula made of two portions, introduced into the straight segment of the ureter. That part of the cannula between which the vessel wall was clamped was made of half cylinders, the perpendicular cylindrical portions being set nearer one end of each than the other.

(*B*) A trocar with a blunt obturator was introduced into the renal pelvis and pushed through the cortex and medulla of the kidney so that it just entered the renal pelvis.

In the paper on the peristalsis of the ureter two tracings were reproduced for the purpose of illustrating the regularity and persistence of ureteral peristalsis. At that time no significance was attached to the fact that, although the tracings were registered by a water manometer, the curve recorded a minimum of 3 mm. and a maximum of 5 mm. positive pressure in the straight portion of the ureter. Throughout the entire period of the three hours that intervened between the two tracings, a constant pressure of 11 cm. of urine was maintained at the distal end of the ureter[17] connected with a vertical glass tube from the upper end of which the urine escaped. In that particular experiment the trocar was not introduced into the renal pelvis. The observation suggests, however, that there was no transmission of pressure to the kidney through the ureter.

In fourteen experiments in which the trocar was placed in the renal pelvis an L cannula was inserted at the same time in the straight portion of the ureter at various locations between the isthmus and the bladder, and pressure was exerted in the outlet cannula (inserted just above the bladder) by one of the following three methods:

[16] Sollmann: This journal, 1905, xiii, p. 243.

[17] Lucas: This journal, 1906, xvii, p. 397, 1 *a* and *b*.

(*A*) The urine was allowed to collect in a vertical tube.

(*B*) The outflow was blocked by clamping.

(*C*) Fluid was injected through a T cannula, one end of its horizontal arm transmitting the pressure into the ureter, the other to a perpendicular glass tube to which was strapped a metre stick to facilitate the reading of pressure.

Almost without exception, in the experiments that were conducted without mishap, pressure up to 15 cm. did not cause elevation of the pressure recorded from the straight portion. The pressure in the pelvic portion almost invariably manifested a tendency to decrease, although under these conditions contraction waves were seldom recorded from the pelvis. When pressure higher than this was exerted, a rise of pressure was frequently recorded from the straight portion, the contraction waves becoming often less frequent, sometimes more frequent, at which time the tendency to a higher pressure record from the L cannula was less pronounced. Even at this time the trocar, as a rule, recorded zero pressure in the renal pelvis. Nevertheless small, very rapid undulations frequently began to appear on the pelvic tracing (Fig. 2), and if the pressure was maintained for a time, or if the ureter was subjected to deleterious conditions such as exposure to cold or desiccation, or if chloroform or any other muscular depressant was administered, the pelvic curve showed the tendency to development of a positive pressure, while the straight portion exhibited larger and larger waves, at less frequent intervals, on which smaller waves were often superimposed.

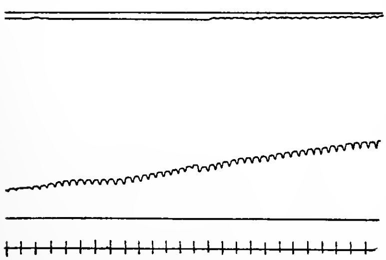

FIGURE 2. Lower tracing, time in seconds. Second tracing, base line for pressure in the straight portion of the ureter. Third tracing, pressure from the straight portion of the ureter. Fourth tracing, pressure from the renal pelvis. Fifth tracing, base line for pressure in the renal pelvis.

When, however, the pressure was permitted to continue for a sufficient time or increased, or if deleterious drugs were allowed to influence conditions, a sudden drop of pressure in the straight portion occurred synchronously with an abrupt rise in the pelvic pressure. Both pressures returned quickly to their previous levels, — the ureter pressure by short, step-like ascents, the pelvic pressure by shorter and more rapid descents (Fig. 3). The pelvic pressure

usually became neutral, the curves often entirely disappearing, the phenomena recurring again and again, tending to become more frequent; but recurrence was by no means regular. Quite often the large ureteral curves were not accompanied by the large pelvic curves.

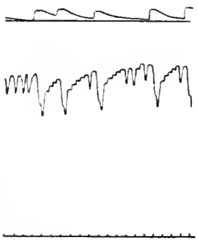

FIGURE 3. Lowest tracing, time in seconds and base line for the pressure in the straight portion of the ureter. Second tracing, ureter pressure from straight portion. Third tracing represents the base line for the pressure curve of the renal pelvis. Fourth tracing, pressure from renal pelvis. The more rapid oscillations in the pelvic curve do not show in the figure.

FIGURE 4. Continuation of Fig. 3, thirty minutes later. Lower line, base line. Second tracing from bottom, from straight portion of the ureter. Upper tracing, from renal pelvis.

However, large pelvic curves never appeared under these conditions unaccompanied by decided increase in the size of the ureteral curves, but large pelvic curves could be induced previous to the appearance of, or unaccompanied by, the large curves of the straight portion, by rapidly infusing into a femoral vein 100 to 200 c.c. of warm physiological salt solution. Following the large pelvic curve thus produced, the curves of the straight portion, as a rule, became smaller and more frequent for a time, but subsequently the larger ascents and descents took place again. I am quite sure that the drops in pressure in the straight portion were due to fatigue and relaxation of the ureter; also that the synchronous rises in pressure in the pelvic portion, when they occurred, were due to reflux of urine into the renal pelvis, and the return to normal pressure brought about by the recovery and natural peristaltic action of the two portions.

When, however, the pressure was maintained or increased, or the action of deleterious agents brought to bear on the ureter, the large curves registered in the two portions became higher and the period of return to their previous levels was more prolonged. Subsequently, if the above-mentioned deleterious influences were continued, the

ureteral curves became more rapid, smaller, and regular. The pressure in the straight portion decreased and the tendency to production of large curves disappeared. The pelvic pressure increased, however, the curves recording it becoming larger and more regular. These curves from the two portions continued quite regularly for a long time, but occasionally a large ascending curve occurred in the ureteral tracing synchronous with a large descending curve from the pelvic tracing (Fig. 4). This, I believe, was not an evidence of further fatigue, but a manifestation of a tendency to recovery, and illustrates what I think occurs under normal conditions, but which I have been unable to demonstrate with my crude technique, *i. e.*, the tendency of the ureter, by its peristaltic action, to dispel or withdraw from the renal pelvis and kidney all pressure that would tend to arise from the collection of urine in the renal pelvis, perhaps even in the uriniferous tubules. Not infrequently, as before stated, a slight degree of negative pressure was recorded from the renal pelvis at the beginning of different experiments when the ureter was contracting actively. Such a negative pressure would explain also why, under my experimental conditions, no pressures could be recorded through the trocar connected with a water manometer, for the exertion of a counter suction caused by the column of water in the manometer would draw the ureter wall against the end of the trocar cannula and thus effectively prevent any variations of pressure from being transmitted.

It may be advisable to mention that when membrane tambours were used in place of water manometers, depressions in the pelvic curve were frequently noted to be synchronous with contractions of the straight portion of the ureter, even when fine undulations were not transmitted from the renal pelvis. It seemed, too, that the drop in pelvic pressure coincided closely (when inspected with the naked eye at the time the tracings were being recorded) with the longitudinal motion of the ureter.

Analysis of some of the experiments on animals successfully used for study in situ of ureteral pressure. — The phenomena produced under these experimental conditions, which appear to be constant and which, I believe, represent closely normal states, are the following: In four different animals there was a slight degree of negative pressure in the renal pelvis. At that time, in these experiments, the pressure in the straight portion varied from 0 cm. to 10 cm. of water, positive. In other experiments a negative pressure in

the straight portion of the ureter existed to the extent of 4 cm. The difficulty encountered in recording negative pressure from the renal pelvis was also met with in recording the pressure in the straight portion. However, the shape of the cannula may have furnished a condition slightly more favorable; its rigid half-cylindrical walls may have prevented the collapse of the ureter wall against the outlet tube to the manometer.

In two experiments showing positive pressure in the renal pelvis at the beginning of the experiment (in one, 8 cm., in the other, 6 cm. pressure) a kink in one of the tubes was subsequently detected which, on removal, allowed the pressure to fall and was without doubt the cause of the high pressure recorded. In four experiments neither negative nor positive pressure was recorded, nor were any contraction waves transmitted until positive pressure was caused by infusion or blocking the outflow of urine. These results demonstrated that the connections and ureter were patent. I am inclined to believe that the above-mentioned neutrality of pressure was due to the fact that the contractions acted so efficiently in carrying the urine away from and past the cannulas that there was lacking the minimal positive pressure necessary for the production of curves.

As a rule, increased pressure in the renal pelvis, whether caused by rapid infusion of physiological salt solution into a large vein of the animal, or by injection with a syringe through the wall of the rubber tube connection between the trocar and manometer, promptly increased peristalsis. The latter increased directly as the pressure, shortly afterward regaining the previous frequency and extent. The fact that in the straight portion the peristaltic rate was not so great, even when the pressure in this portion was still rising, *after* the injection of solution had been discontinued, suggests that the flow of fluid along the ureter under such conditions may also tend to act as a stimulus to the contractions aside from that induced by its distention.

Although as much as 500 c.c. of physiological salt solution was infused, in 100 c.c. amounts, at intervals of thirty minutes or less, into dogs weighing about 25 kilos, the ensuing increased flow of urine was very marked, but only a temporary rise of pressure in the renal pelvis and straight portion was noted. There was, of course, an immediate rise of blood pressure. In the renal pelvis the pressure increase occurred simultaneously with the infusion, disappearing very shortly after the infusion was stopped. Rise in

the straight portion was somewhat slower, higher, and of longer duration. The usual stimulation of ureteral contractions during the increase of pressure was noted, and it was found that, without exception, the pressure quickly returned to the one recorded previous to the infusion. In fact, the saline infusions, under conditions where the resistance to the outflow was not too great, seemed to favor peristalsis more decidedly and to cause a diminution of intra-ureteral pressure.

Conclusions. — I believe these experiments indicate very strongly that under normal conditions the intra-ureteral pressure remains at zero. The amount of urine in the ureter that ordinarily is necessary to call forth peristalsis is probably so slight that it causes scarcely any pressure in the relaxed ureter, and in the case of normal peristalic contraction directs the urine into the bladder. At the same time a tendency to the production of negative pressure is doubtless exerted behind the mass of urine that proceeds downward. The flaccid muscular walls would be collapsed by such a negative intra-ureteral pressure, however. A mechanism by which negative pressure could be attained to an appreciable degree in the straight portion is difficult to conceive. In the renal pelvis conditions are somewhat different. In the first place the shape of the ureter above the isthmus becomes more and more flared. This portion is held open by its attachment to the firm kidney substance. Again this portion is abundantly supplied with nerves. From my observations of the action of this portion of the ureter, I am inclined to believe that here conditions prevail which are less favorable to accumulation of urine and more favorable to a negative pressure. However, there are other phenomena than those already mentioned that indicate highly co-ordinated and purposeful actions of this portion.

From the above observations, based as they are on experimental study, it appears that the ureter is specially antagonistic to transmission of pressure towards the kidney. The portion of the ureter above the middle, unenervated third, is apparently even more efficient in its resistance than the lower portions. The pressure necessary to overcome this action, under the above-mentioned conditions of experimentation, is somewhat above that produced by a 30 cm. column of water, and varies naturally with the duration of application, drugs used, exposure, size of animal, etc.

III. Ureteral Pressure and Renal Circulation.

Introductory. — The experimental results already recorded here indicate that the ureter is more than a simple conducting tube. It not only carries urine away from the kidney and discharges it into the bladder, but by its peristalsis it also prevents collection of urine in the renal pelvis, thus inducing a condition favorable to continuous flow from the tubules and spaces of Bowman's capsules. This state of affairs brings to mind a much studied problem, namely, the nature of urinary secretion.

The physical phenomena in the secretion of urine have recently been extensively studied by Sollmann,[18] who states with accuracy, "a knowledge of the mechanical phenomena occurring in the kidney would seem to be a necessary prerequisite to the discussion of any theory of urine secretion."

It is obvious that any influence the ureter may exert on the kidney must be primarily mechanical. Therefore I have made a study of certain mechanical phenomena in urinary formation, with the ureter and the glomeruli of the kidney especially in mind as influencing factors.

Experimental. Methods. — In these investigations I have followed in a general way Sollmann's technique for perfusing excised kidneys. I am indebted to Professor Sollmann for important suggestions in this connection. My experiments differ chiefly from his in that most of his work was done on kidneys in which the vital action was very largely excluded and the action of the ureter given little attention, while I have tried to control the mechanical phenomena to as large a degree as possible by removing the kidney and ureter from the animal, at the same time endeavoring to maintain the vital action of the ureter.

I have also performed a number of perfusion experiments by Sollman's technique exactly, in order to test his methods. Finding that my results confirmed his observations and conclusions, I based many of my tests and observations on his analogous data.

The vitality of the kidney and ureter is very persistent. — Sollmann presented evidence showing that a certain degree of vitality is maintained by the excised kidney for many hours. His experiments and conclusions applied to both the vitality of the se-

[18] Sollmann: This journal, 1905, xiii, p. 241.

cretory epithelium and the blood vessels. His results for the vessels are classified under the heads: (1) Dilator reaction; (2) Adrenalin reaction; (3) Hydrocyanic acid reaction. Sollmann's experimental results show that the vessels maintain vital activity to some degree two days after excision.

As I stated before, my attention has been directed in this research to the vascular system of the kidney and to the ureter. I have confirmed the results of Sollmann on the vessels, and have investigated, in addition, the effects of the following on the ureter and on the vessels of the kidney: adrenalin, barium chloride, caffein, diuretin, chloral, chloroform, magnesium sulphate, physostigmin, atropin, pilocarpin, cocain, sodium chloride, oxygen, carbon dioxide, cerium nitrate, heat, cold, mechanical irritation and electricity.

My observations of the effects of the above-named substances and conditions will be taken up in detail in the fifth section of this paper. It is sufficient to state here that the vessels of the excised kidney and the ureter are susceptible to the influence of drugs for many hours after excision.

In the living animal there are many conditions that influence the renal circulation. The following technique was used to eliminate such undesirable influences as changes in general blood pressure and nervous control.

The animal was anesthetized with ether or the skin over the femoral artery cocainized, the artery exposed and cannulized, and the animal bled to death. An incision was then made along the linea alba from ensiform cartilage to symphesis pubis and, by transverse cuts, extended from the first wound through the abdominal muscles to the dorsal region, passing just below the last rib. The ureter, kidney, and bladder were exposed by retracting the other abdominal viscera in warm towels. The artery of the kidney to be studied was exposed and cannulized with as large a glass cannula as could easily be inserted. This was filled immediately with warm Ringer solution, and, by means of a ten-ounce hand syringe joined to the cannula by a short piece of rubber tubing, the kidney vessels were flushed with Ringer solution at 38° C. until the vein flow was seen to be clear. The vein was then cannulized. A trocar cannula was introduced and retained in the renal pelvis, and an L cannula inserted into the straight portion of the ureter. If the ureteral flow was to be noted or the effect of injection into it studied, a small straight glass cannula was inserted just above the bladder

and the ureter severed below the cannula. The kidney and adjacent vessels and cannulas, with the ureter, were removed to a bath of Ringer solution maintained at a constant temperature of 38° C.; the artery was connected to a perfusion apparatus consisting of a 20-litre bottle, filled with Ringer solution and fitted with a Mariotte tube for maintaining constant pressure, and elevated to such a height that an injection pressure of 122.5 cm. was constantly maintained. A litre flask was inserted in the system and placed in a water bath, by means of which the temperature of the injection fluid could be kept constant. A thermometer inserted through the vertical arm of a T tube just proximal to the point of injection indicated the temperature of the perfusing fluid at its entrance to the artery, which temperature was maintained at 38° C. The cannula in the straight portion of the ureter and the one in the renal pelvis were each connected to a membrane tambour. This tambour was adjusted to write on the revolving smoked drum of a kymograph on which the time was marked in seconds, and the rate of vein flow recorded in drops from the vein cannula allowed to fall on the paddle of a Marey tambour. The outlet cannula of the ureter was connected by means of a T tube to a perpendicular tube by which the rate of flow or the resistance of flow to artificial pressure could be varied at will.

Results. — The fifth experiment being representative, it will be used as illustrative of the phenomena thus far observed by this method. In this experiment the outlet cannula of the ureter was connected with the perpendicular tube for the purpose of causing automatic increase of pressure at the distal end of the ureter.

5. February 18, 1908. — On opening the arterial clamp the kidney became tense, the vein flow started immediately and was very free — twelve drops per second. The pressure in the renal pelvis rose abruptly as the injection fluid entered the kidney. The pressure was slight and showed no tendency to change for several hours. No contraction curves were registered from this portion of the ureter until later, when the straight portion was overcome by pressure and fatigue.

   The pressure in the straight portion of the ureter remained at zero for ten minutes, no peristaltic waves being recorded. At the end of that time a very slight rise in the intra-ureteral pressure of the straight portion was noted, when the peristaltic waves began abruptly and continued at the rate of one in ten seconds, tending

to increase in rate as the pressure rose, until the pressure reached 18 cm., when the curves became larger and slower.

After the rapid primary flow from the vein had reached its maximum there was a gradual decrease as the time of perfusion advanced. In what Sollmann [19] describes as the third stage in perfusion of the excised kidney, at the point where the vein flow remains almost constant (Fig. 5), there was a tendency at times when the ureter action was most efficient, toward an increase in the vein flow (Fig. 6).

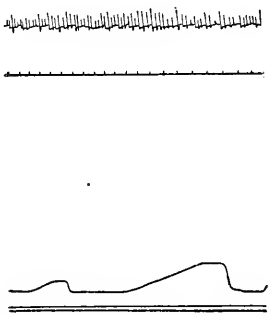

FIGURE 5. Upper tracing, vein flow in drops. Second tracing from top, time in seconds. Third tracing from top, ureteral pressure through the cannula in the middle of the straight portion. Fourth tracing from top, pressure from renal pelvis. Lowest tracing, base line for both pressure curves. The tracings were recorded two hours and ten minutes after perfusion was started. The number of ureteral contractions during the last thirty minutes of this time averaged 56.1 per ten minutes; the vein flow per ten minutes, 2056.8 drops (124.4 c.c.).

FIGURE 6. Same as Fig. 5, obtained twenty minutes later, the resistance to the ureteral outflow having been increased in the meantime from 5 to 10 cm. of water. Ureteral contractions averaged 109 per ten minutes. Vein flow, 3840 drops (228.5 c.c.) in the same time.

When relaxation and inactivity of the ureter took place, there was a marked decrease of the pressure in the straight portion of the ureter which was transmitted to the pelvic portion; at the same time the vein flow was abruptly reduced from 10 to less than 1 drop per second (Fig. 7). When the intra-ureteral pressure was rapidly increased by injection of Ringer solution through the outlet cannula, the primary effect of the increasing pressure in the renal pelvis was an increased vein flow (probably due to expression from the renal vessels). The vein flow then steadily decreased as the pressure increased. When a maximum pressure of 38 cm.

[19] SOLLMANN: This journal, 1905, xiii, p. 249, Fig. 2.

was caused in a period of twelve seconds, the above-described phenomena were noted in spite of the maintenance of this maximum pressure, and the vein flow again tended to increase rapidly, but in the succeeding ten minutes did not attain the rate noted previously to the inauguration of the pressure (Fig. 8). Again, if the above-mentioned pressure was obtained by six separate injections at intervals of ten to fifteen seconds, the retardation of the vein flow was much less distinct.

IV. Ureteral Pressure and the Flow of Urine.

Introductory. — The results of many of my experiments have led to the conclusion that the ureter acts in an antagonistic manner to pressures toward the kidney, and that this action of the ureter not only protects the kidney from pressure caused by accumulation of urine in the renal pelvis, but also encourages the flow of blood throughout the kidney.

Inasmuch as the ureter influences by its action or non-action the flow of blood throughout the kidney, the ureter must, to that extent at least, influence the flow of urine. In some of my experiments I observed that, in the excised ureter and kidney, the ordinary relation between them was somewhat different from any noted when *in situ*. The present study has been carried out on the kidney and ureter in their normal relationships in order to determine more intimately, if possible, the ureteral influence on urinary flow.

Methods. — The animal was kept on a soft or liquid diet for several days, then narcotized by hypodermic injection of morphine, placed in a dog-holder,[20] and shaved dorsally from the last rib to the crest of the ileum on each side. An incision was made from the angle between the last rib and vertebral column, extended down and outward, and the ureter in its middle or lower third was exposed retroperitoneally. A small glass cannula was introduced into the ureter, which was severed below the cannula and brought to the edge of the wound, the wound closed by interrupted sutures, and the ureter fixed by attaching it, by a slight stitch in its wall, to the surrounding muscle. The urine from each ureter was caught in a 100 c.c. graduated cylinder and saved for examination. The normal rate of flow from each kidney was recorded. When this had been satisfactorily determined, one of the ureteral cannulas

[20] Meyer: This journal, 1907, xxix, p. 906.

was joined to a perpendicular glass tube of small calibre by the side of which a metre stick was fastened. The other cannula was not interfered with, nor was the ureter disturbed by the adjustment of connections. Thus the effect on the ureter and kidney of gradually increasing pressure caused by the secretory activity of a kidney, as well as the continuance of flow from each kidney, was observed.

Deductions regarding transmission of ureteral pressure to the kidney were made (*a*) from the aspect of the undulations brought about by the contractions of the ureter caused in the vertical tube

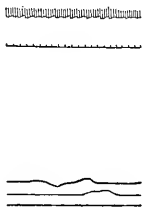

FIGURE 7.

FIGURE 7. Same as Fig. 5, four hours after perfusion was started. Peristalsis infrequent and irregular, ureter relaxing at times, allowing pressure to be transmitted to the renal pelvis. Vein flow averaged 1510 drops (94.25 c.c.) per ten minutes.

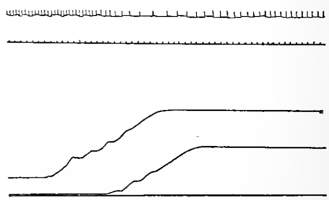

FIGURE 8.

FIGURE 8. Same as Fig. 7 (later). Peristalsis having ceased, ureteral pressure rapidly increased to 38 cm. (of water).

through which the pressure was exerted; (*b*) from changes in the amount and composition of the urine, and (*c*) from the results of *post mortem* examination of the kidney.

The cannulas were maintained in the ureters two or three days, at the end of which time they ceased to remain in place, because of pressure necrosis of the ureter due to the retaining ligature at the point of insertion into the ureter. The animal was continuously protected from pain by small though sufficient doses of morphine. Readings were made on each day for periods of three to five hours.

Inasmuch as the results obtained on the first days of Experiment No. 2 are typical, they will be cited by way of illustration.

Results. — The curves of Fig. 9 show two distinct effects of pressure on the rate of flow, *i. e.*, a decided increase between pressures of 2.5 and 25 cm., and a decrease commencing as the pressure rose above the 25 cm. mark. At the time of experimentation it was noted that while the flow was increased as the pressure rose in the perpendicular tube towards the 25 cm. mark, the meniscus rose and fell in a rapid and regular manner, which fluctuations, had the

pressure been recorded by the graphic method, would have given a curve of the character shown in Fig. 2 (third tracing from the bottom). I believe the intra-ureteral pressure conditions represented by the figure referred to are entirely analogous to those attained by the above-mentioned method, *i. e.*, the pressure exerted at the ureteral outlet is not transmitted to the renal pelvis, therefore does not act on the kidney, as such, although the stimulation of the ureter may have an indirect effect on the kidney.

When the column of urine nearly reached the 25 cm. mark, the oscillations became greater in extent and irregular in rate. The same pressure also caused retardation of the flow of the urine. The oscillations of pressure, if recorded at that time, would have exhibited a curve of the type shown in Fig. 3 (second tracing from the bottom). The oscillations indicated, I think, the time at which the ureter muscle was succumbing to the pressure and fatigue. At that point, for the first time, pressure as such exerted at the outlet of the ureter was transmitted through the ureter to the kidney. I do not believe that even at that time the pressure was transmitted in its entirety. Furthermore, its action was probably only for brief periods.

The column of urine continued to rise and oscillate in the above-mentioned manner until, after a time, the pressure approached 50 cm., when again the type of oscillation of the column of urine gradually changed to that represented by the curve in Fig. 4. This curve is characterized by the sudden falls of pressure and the more gradual returns to the previous levels, by very small and rapid oscillations, as shown by the second curve from the bottom of Fig. 4.

As the pressure increased from 50 to 67 cm. the fluctuations became smaller, being of the type shown on the ascending portion of the curve in Fig. 3. As the pressure gradually rose during this period, fluctuations of greater extent occasionally appeared, as is shown in Fig. 4.

After the column of urine reached the 65 cm. mark, there was no further ascent during the remaining thirty-six minutes of observation, the oscillations in the pressure tube also disappearing.

Without exception, in these experiments slight pressure, *i. e.*, from 2.5 to 25 cm., was accompanied by increased flow of urine from the ureter in which the pressure was exerted. The results of previous experiments on the ureter, compared with the oscillations of the fluid in the pressure tube in these experiments, make

me certain that pressures exerted in the ureter between 2.5 and 25 cm. were not transmitted as such to the renal pelvis. It is probable, however, that pressure between 25 and 50 cm. may have been transmitted to a slight degree at moments of relaxation of the ureter, when the abrupt drops in the column were noticeable.

The behavior of the ureter, when the pressures varied between the 50 and 67 cm. marks, suggests that its resistance was overcome, and that such pressures were transmitted almost entirely to the kidney, under which condition there was absolute stoppage of the urine flow from that kidney during a period of eighteen minutes.

The animal was then returned to its cage at 4.30 P. M. (October 12, 1907), and given food and water (500 c.c.).

The curve plotted from the rate of ascent of the urine secreted in the vertical tube is shown in Fig. 9.

The total amount of urine excreted between 4.30 P. M. (October 12, 1907) and 9 A. M. (October 13, 1907) was 175 c.c., at which time the animal was given 500 c.c. of water. At 10 A. M., 0.044 gm. of morphine were injected hypodermically. At 10.45 A. M., 350 c.c. of clear material was vomited. When the animal became thoroughly narcotized, it was again placed in the dog-holder, and at twelve o'clock the collection of urine was begun. The urine from the left kidney was clear and reddish, while that secreted by the right kidney was clear and yellowish.

The rate of flow from each kidney was recorded as follows:

Time of observation.	Urine from right kidney.	Urine from left kidney.	Remarks.
	c.c.	c.c.	
First 30 minutes	6.20	6.15	The urine was allowed to flow from the ureteral cannulas without resistance.
Second 30 minutes	4.80	4.85	
Third 30 minutes	4.00	4.00	
Fourth 30 minutes	2.90	....	The ureter from the left kidney was attached to a vertical tube; the right, as above.
Fifth 30 minutes	2.20	3.50	
	No albumin.	Albumin present.	
	Sp. gr. 1 0245	Sp. gr. 1.0277	

V. Biochemical Influences on Ureteral Pressure.[21]

The ureter is a highly specialized, involuntary muscular organ, and has been the fruitful subject for many investigations of the myogenic and neurogenic origin of automatic muscular contractions.

[21] Some of the experiments of this section were performed in the Department of Pharmacology in this institution under the direction of Dr. A. N. Richards, to whom I am indebted for much assistance.

The conclusions of such studies of the ureter have often been applied to the beating of the heart and to the movements of the intestines and other organs largely made up of smooth muscle fibres. However, the extent of the nerve supply of the middle portion of the ureter is a debatable question (Englemann, Dogiel, and others).

Protopow made an extended study of the separate existence of the requisite elements for muscular contractions.[22] He used the ureter as the subject of his investigations, which were both histological and biochemical in nature. He concluded that the requisite elements for muscular movements are found separately in the ureter of man and the higher animals. He also stated that stimulating the splanchnic

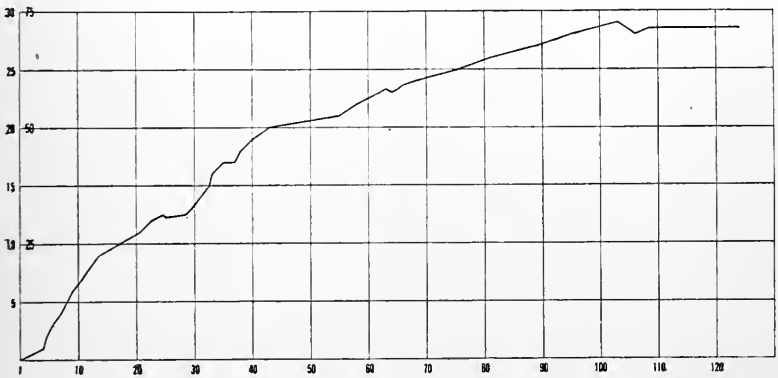

FIGURE 9. The curve is constructed from the records of the time required for the excreted urine to make successively an advance of one inch in the vertical tube; increasing pressure is automatically exerted by the rising column.

nerves has a motor effect on the ureter. Fagge[23] pointed out that stimulation of the hypogastric nerve has a motor effect on the portion of the ureter adjacent to the bladder.

Of more purely biochemical nature are the researches of Stern,[24] Hedon and Fleig,[25] Manevitch,[26] Pugliese,[27] and others, in which the control of automatic movements of the ureter by various cations and anions has been extensively studied. Hedon and Fleig investigated especially the effects of the ions which are found in the various artificial blood sera.

[22] PROTOPOW: Archiv für die gesammte Physiologie, 1897, lxvi, p. 1.

[23] FAGGE: Journal of physiology, 1902, xxviii, p. 304.

[24] STERN: Thèse de Geneva, 1903.

[25] HEDON et FLEIG: Archives internationales de physiologie, 1905–1906, iii, p. 95.

[26] MANEVITCH: Revue médicale de la suisse romande, 1907, xxvii, p. 585.

[27] PUGLIESE: Archives italiennes de biologie, 1906–1907, xliii, p. 54.

Manevitch divides the cations which affect the contractions of the ureter into three groups: (1) Those which have the power of preserving to the highest degree the automatic contractions of the excised ureter (smooth muscle tissue), *e. g.*, Na and Li; (2) Those which depress the tonus and stop the rhythmic and automatic function of smooth muscle, K, NH_4, Mg, Zn, Cd, Pb, Co, Ni, Fe, Mn, Cu; (3) Those which are stimulants to the tonus, and aid development of the rhythmic and automatic action of smooth muscle, foremost among which are Ba and Sr. Ca, according to Manevitch, occupies a special place, having some of the characters of barium and strontium. It causes a development of deficient automatic contractions, and renders better, and more energetic, the contractions already in progress, but, on the other hand, often tends to inhibit or retard the rhythm.

The cations Sr and Ba are conceded by Manevitch to be antagonistic, in their action on smooth muscle tissue, to those of the second group named above, *i. e.*, to K, NH_4, Mg, etc. Manevitch also states that when the automatic contractions of the ureter have become greatly diminished after hours of action in solutions containing indifferent cations such as Na, Li, Cl, they are again greatly revived by solutions containing Ba or Sr cations.

From a study of the literature, one sees that the activity of the ureter must be greatly influenced by chemical as well as nervous influences. It seems probable, then, that a study of the influence on the ureter of chemical substances which occur as normal constituents of blood and urine compared with the effects of substances appearing in these liquids when used as drugs that act on the kidney (and ureter?), may give us information concerning both the function of the ureter and the action of drugs. The specific influence of drugs on the ureter in a normal animal cannot be precisely controlled. However, their influences can be determined by excising the organ and placing it in one of the artificial blood sera whose action has been definitely ascertained. After such a determination the influence of drugs under ordinary conditions can be satisfactorily recognized with due regard for other vital processes affected by them.

Experiments on the excised ureter. Method. — Usually a cat or small dog was chosen, which was anesthetized with ether, or bled to death. The portion of the ureter to be studied was quickly isolated and removed to a bath of warm physiological salt solution, where

the adjustments of such cannulas and apparatus as were to be used in the particular experiment were made, one of the three following methods of procedure being used:

(*A*) The isolated piece of ureter was ligated at both ends, one end anchored at the bottom of the bath, the other to a writing lever which traced on a smoked drum.

(*B*) The anchorage of the ureter was attained by inserting the end of a curved glass cannula into the lumen of the lower end, through which warm physiological salt solution was injected for the production of any desired intra-ureteral pressure. The effects of the contractions were not only recorded on the drum as in method *A*, but could also be noted in the fluctuations of the fluid in the vertical pressure tube.

(*C*) The ureter was placed horizontally in the bath, a cannula inserted in each end as in method *B*, and a myocardiograph attached to the ureter as for recording contractions of the heart.

The effect of *barium chloride* on the ureter is illustrated by Experiment 1, which was performed by technique *A*.

1. October 27, 1907. — Medium-sized cat, killed by decapitation. The middle third of one ureter and a section of the small gut of the same length as the section of ureter were excised, ligatures tied to the ends of each, the sections anchored at the bottom of a beaker containing Locke solution at 40° C. (through which oxygen bubbled constantly), and the free end of each attached to a spring writing-lever which traced on a revolving smoked drum.

   The gut began to record contractions immediately, the ureter remaining perfectly motionless for forty minutes, at the end of which time 1 c.c. of 5 per cent barium chloride was added to the 40 c.c. of Locke solution contained in the bath. The intestinal contractions were immediately increased greatly. The ureter made its first contraction thirty seconds after the addition, which was followed by contractions occurring every twenty-five to thirty seconds and showing for a short time a tendency to become stronger. Sometimes the excursion of the recording arm was very great, the succeeding pause being correspondingly lengthened. Later there was a tendency for two contractions to occur in quick succession or for a second to occur before the complete relaxation from the first, the rate of contractions increasing, but the extent of contraction becoming less. As a rule, the period of rest following a double contraction was greater than that following a single contraction of equal extent. The contractions continued to become more fre-

quent and less in extent until they disappeared. Subsequent additions of barium chloride did not cause additional contractions.

The influence of *adrenalin* on the isolated ureter as tested by the same method was exhibited by a pronounced increase in tonus and contractility, but often there was no stimulation of the rate of contraction; in fact the number of contractions was often decreased, as shown in Experiments 2 and 3, protocols of which are appended:

2. December 6, 1907. — An ox ureter, obtained at a slaughter-house immediately after the animal had been killed by the usual method, was placed in a quart jar of Ringer solution at 38° C. and carried

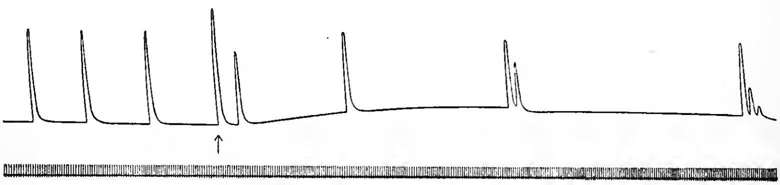

FIGURE 10. Lower tracing, time in ten seconds. Second tracing, contractions of the ureter showing the effect of adrenalin chloride.

to the laboratory, where it was subjected to the treatment of method B. The time that elapsed between the killing of the animal and the completion of all manipulations was about forty-five minutes.

During transportation of the ureter the solution in which it was immersed cooled to 35° C.

No contraction appeared during the first ten minutes after the application of method B, at the end of which time 1 c.c. of a 5 per cent solution of barium chloride was added to the bath of 500 c.c. of Ringer solution. Fifty seconds later the first contraction was recorded. It was followed by other contractions at gradually increasing intervals of from two seconds to two minutes. When the contraction rate had become one in about two minutes, 0.2 c.c. of 1:1000 adrenalin solution were added to the bath, whereupon the rate of contraction was distinctly decreased; but the line that was traced when the ureter was at rest gradually rose for fifteen minutes, regardless of the contractions which had begun to show a tendency to occur in groups of twos or threes (Fig. 10).

3. December 13, 1907. — Small dog. Etherized. A femoral artery was cannulized and the dog bled to death. The ureter was removed and placed in 500 c.c. of Ringer solution. Method B was

applied. No intra-ureteral pressure was exerted, and only one contraction took place during the first twenty minutes, which seemed to be the result of irritation caused by handling the ureteral cannula. The intra-ureteral pressure was then increased to 68 cm. Contractions immediately appeared, and recurred fairly regularly. The pressure was lowered to 50 cm., the extent of contraction becoming greater but the rate remaining about the same. The contractions continued regularly at this rate for forty-five minutes, when 0.2 c.c. of 1 : 1000 adrenalin solution was added to the bath of 500 c.c. of Ringer solution. The contractions continued at the previous rate for thirty-five seconds longer, then eleven contractions occurred in the succeeding thirty-eight seconds. After the last of these, no contraction occurred for twenty-five seconds, when a curve resulted which was composed of three contractions and reached a height about twice that of any previously recorded. This curve was followed by others of like character at the rate of one per minute, but after the first three of decreasing size and increasing rate, the curves showed an increasing tendency of the contractions to occur in groups (Fig. 11).

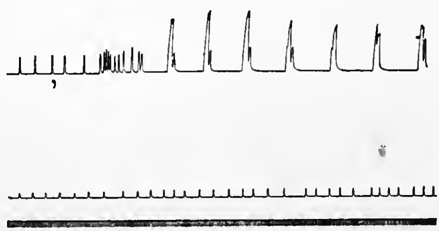

FIGURE 11. Lowest tracing, time in ten seconds. Second tracing, ureteral contractions by method *B* (where an intra-ureteral pressure of 68 cm. Ringer solution prevailed). Third tracing, intra-ureteral pressure had been reduced to 50 cm. at the mark (,) 0.2 c.c. of 1 : 1000 adrenalin solution was added to the bath of 500 c.c. of Ringer solution.

In other experiments with the same technique, where the contractions were very infrequent or entirely absent, a slightly larger dose of the adrenalin than those used in the experiments described in the preceding protocols caused a tonic contraction which did not show any tendency to relaxation after sixteen minutes, whereupon the bath was changed to plain Ringer solution. The muscle then gradually relaxed, returning in five minutes to its original state.

It seems, from the results of the experiments with adrenalin, that this substance increases both the contractility and the tone of the ureter muscle.

Caffein produced phenomena very similar to those caused by adrenalin. *Diuretin* also acted in a similar way. *Chloral, chloroform, ether,* and *magnesium sulphate* were distinctly depressant, showing at times a slight preliminary irritation.

In the experiments with the excised ureter by the method described above, *nicotin, atropin, muscarin,* and *physostigmin* gave only negative results (but I feel confident that these drugs exert definite influences and that they can be demonstrated graphically by improvement of the technique).

The ureteral contractions seemed to be developed less satisfactorily in oxygenated solutions than in unoxygenated ones.

The results of this study of the effects of drugs on the *excised* ureter warrant the following conclusions:

1. Adrenalin, caffein, and diuretin increase the tone and contractility of the ureter muscle.

2. Barium chloride increases the irritability more noticeably than the substances of the first group, and does not seem to have such pronounced influence on the tone, unless it is to depress it.

3. Chloral, chloroform, ether, and magnesium sulphate exert at first slight irritating action, but later cause marked depression.

These observations on the excised ureter cannot be exactly applied to the complete ureter, however, for the middle third was usually employed in these tests. Nerve influences would be much less prominent in this portion than in other portions.

Experiments on the ureter in situ. *Method.* — Dogs were used for all of these experiments. Chloroform or ether was employed only for the purpose of studying effects upon the ureteral peristalsis. The animal was narcotized with morphine, and the ureter exposed by an incision along the linea alba from symphysis pubis to ensiform cartilage. The abdominal walls were then retracted, the intestines were drawn to one side, and the viscera as well as the rest of the animal were covered with warm towels and cotton. The kidney was exposed by another incision along the lower border of the last rib, or by a small longitudinal incision directly over the kidney. The left kidney was usually selected on account of its lower and more accessible position.

Graphic representations of the ureteral movements were obtained as usual with a water manometer, the undulations of the column of water being transmitted by means of a float and style to a revolving drum. The connections with the ureter were made by two methods:

(*A*) By introducing into the ureter a cannula which is a modification of the Ludwig-Spengler artery cannula. With this cannula a much smaller incision than usual is required; no ligation being necessary, the propagation of the muscular wave of the ureter is only slightly interfered with, the nutrient vessels of the ureter can be avoided, and the nutrition of the ureter is only slightly impaired.

(*B*) By introducing a trocar through the kidney into the renal pelvis, and retaining it in place by a purse-string suture around the point of puncture of the capsule of the kidney. This also helped to stop bleeding, which, however, was surprisingly slight. A small quantity of warm salt solution or urine aspirated fresh from the bladder was injected through the needle; thus the patency of the cannula and ureter was ascertained.

In connecting the cannulas with the water manometer by means of narrow glass and rubber tubing, urine was separated from the water in the manometer by a column of air. Any movement of the urine caused an undulation in the manometer. These undulations were recorded on a drum by means of an Emerson float.

In most of the experiments of this series the ureter remained in normal connection with the bladder. In some experiments, however, the ureter was severed near the bladder, the urine escaping into the abdomen or being carried out of the body by a glass tube connected with the cannula in the ureter. This cannula narrowed, of course, the lumen of the ureter, and thus afforded some resistance to the flow of urine out of the ureter. In some of the experiments the urine was caused to drop on a pan connected with a Marey tambour, by means of which the flow of urine was recorded.

The dose of morphine varied from 0.06 to 0.12 gram, depending on the size of the animal. This was given subcutaneously sixty to ninety minutes previous to the operation. All experiments were commenced in the morning; the animals had not been fed since the previous evening, but they had free access to water.

The susceptibility of the ureter, *in situ*, to the various substances used in this study seemed to be much greater by this technique. *Chloroform*, administered in the respired air, caused marked decrease of both the extent and frequency of the contractions of the middle part of the ureter, and, if continued, completely abolished them. Sometimes, when the administration was brief, the deteriorating effect did not set in until a little while after the use of the anesthetic was discontinued. Shortly after recovery from the evil

effects of the chloroform in some of these cases, another period of deterioration set in as a second after-effect.

Frequently, when *ether* was suddenly exhibited in the respired air (inhaled *per nares,* not by tracheal cannula), a temporary change almost instantaneously appeared in the curve representing the peristalsis of the ureter in the renal pelvis. Sometimes entire cessation of the peristalsis occurred, which phenomenon could also be elicited by sudden irritation of the nostrils with a probe, — an observation very strongly suggestive of a reflex.

Moderate doses of *caffein* caused various effects in the different parts of the ureter, the portion in the renal pelvis regularly contracting in a somewhat tonic manner and causing thereby a very pronounced rise in the pressure for a short time in that part. This pressure appeared to be attainable through the agency of a sphincter-like action of the isthmus of the ureter, which prevented the urine from escaping. The pressure in the straight portion did not exhibit a simultaneous change.

Adrenalin also showed a tendency to disturb the normal pressure relations between the renal pelvis and the straight part of the ureter. It caused a very pronounced positive pressure, very much as caffein does.

Barium chloride seemed to stimulate the contractions of both the upper and lower portions without the same tendency to cause increased pressure in the renal pelvis.

When small amounts of *chloral* or *magnesium sulphate* were injected into the renal pelvis, only a direct depression was shown.

These tests, while very incomplete, show distinctly that the ureter is very susceptible to the action of drugs administered systemically as well as directly. The experiments with chloroform suggest that there may be a double action of drugs on ureteral muscular activity and tone. The first influence on the peristalsis was exhibited so promptly after the administration of chloroform had been begun, that it could hardly have been due to chloroform secreted into the urine in amounts sufficient to affect the ureter directly, although it seems possible that the circulating blood containing the drug might have some such effect. When the chloroform was withdrawn, at this early period, the very pronounced retardation sometimes did not appear until the animal gave indications that the general systemic action was wearing off, thus increasing the impression that drugs act on the ureter not only while circulating in the blood, but also when present in the urine.

From what I can find in the literature, together with impressions obtained in my own studies of the ureter, it seems that drugs which exert stimulating action on the ureter also appear to possess diuretic power to a somewhat similar degree. I think I am correct in saying that drugs which show a depressing action on the peristalsis of the ureter also often exhibit a tendency, when administered systemically, to decrease the amount of urine. These conclusions suggest that stimulation or inhibition of ureteral action may be a factor in the diuresis, or in the diminished flow of urine, caused by drugs having the above-mentioned influences. The solution of this problem presents a great many difficulties. Nevertheless it should be possible to gain some information regarding it by comparing the effects (on the volume of urine eliminated from each of the two kidneys with both ureters intact) of drugs whose influence is eminently diuretic and ureter-stimulating, *e. g.*, caffein, or diuretin, with the flow of urine from each kidney after the ureter of one kidney has been completely eliminated.

This matter was tested in five experiments on dogs as follows:

Effects of drugs on the comparative flow of urine. — The animals were narcotized with morphine and the ureters exposed only at their entrance to the bladder. A small straight cannula was inserted into each ureter at this location, and the urine collected in small graduated glass cylinders. The normal flow was noted and recorded at regular intervals.

The flow from the kidneys of the same animal was found to be usually quite equal. Infusion of 150 to 200 c.c. of salt solution caused an average diuresis of 20 per cent from each kidney over a period of thirty minutes. The actual amount of diuresis varied in the different animals. No attempt was made to maintain uniform conditions in these animals previous to the experiment. The diuresis was usually quite equal from the kidneys of the same animal.

When, however, 1 gram of diuretin, dissolved in 50 c.c. of warm physiological salt solution, was infused in the femoral vein, the increase in urine from each kidney was equal in the same animal, but varied in different animals from between 250 to 300 per cent. After these preliminary tests had been made in each animal, the ureter from one of the kidneys was exposed at the renal pelvis, and a large glass cannula which flared out considerably at its end, so as to hold the portion of the ureter in the renal pelvis wide open, was inserted and retained by means of a ligature. Such a cannula

prevented any influence of the muscular contraction of the ureter on the flow from the renal pelvis and kidney. (Great care was exercised not to manipulate the kidney or interfere with the renal vessels.) The urine was conducted from the cannula into the graduated cylinder, care being taken to make certain that the degree of resistance to the flow of urine from each cannula was equal. This resistance varied from between 2 to 8 cm. in the different experiments, after all manipulation was completed. The rate of flow

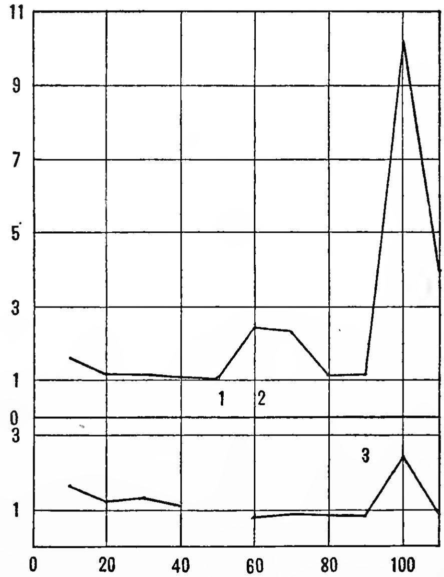

FIGURE 12. Upper curve gives the flow from the left kidney, lower curve that from right kidney. Cannula in renal pelvis. Ureteral action was removed from the right kidney at the end of 40 minutes of observation. The amount secreted was recorded at the end of each 10 minutes. (1) 50 c.c. salt solution. (2) 50 c.c. salt solution. (3) 1 gm. diuretin in 50 c.c. salt solution.

from each kidney was again observed, and as a rule a slight decrease in flow was noted from the kidney cannulized at the renal pelvis. Infusion into a femoral vein of 50 to 100 c.c of physiological salt solution at this stage frequently failed to cause an increased flow from the cannulized kidney, while the flow from the kidney with the ureter intact showed in each experiment an increase of at least 200 per cent. After the flow from the kidney with its intact ureter had returned to the amount eliminated previous to the infusion, and the urine from each kidney was being excreted at a constant

rate, 1 gram of diuretin was infused in 50 c.c. of physiological salt solution. The average increase of the flow from the kidney with intact ureter was 800 per cent for the first ten minutes, falling to 200 per cent in twenty minutes. From the cannulized kidney there was only a 125 per cent increase in the first ten minutes with a return to the normal elimination in twenty minutes (Fig. 12).

Although the damage done by the manipulation when inserting the cannula into the renal pelvis cannot be overlooked as an influence tending to decrease the amount of urine excreted by that kidney, the above observations suggest very strongly a ureteral influence in the diuresis caused by drugs which increase the muscular tone and activity of the ureter.

VI. Summary of General Conclusions.

I. If continued pressure in the bladder exerts a deleterious effect on the kidney, it does so by nervous influence and not by direct transmission of pressure from the bladder to the kidney.

II. Even under the artificial conditions of experimental study, the intra-ureteral pressure tends to remain approximately neutral in the various portions of the ureter. The ureteral pressure is surprisingly strong and efficient when called upon to maintain this intra-ureteral condition.

The effect of the antagonism of the ureter to pressure exerted in it must be carefully taken into account, especially in studies of the effects of artificial pressure through the ureter on the kidney.

The vital activity of the ureter is extremely persistent.

III. Collectively *excised* kidneys and ureters maintain sufficient vital activity, when the kidney is perfused with warm Ringer solution, to permit a study of the relation of the mechanical influence exerted by the ureter on the circulation of the kidney. Under these conditions the ureter is less susceptible to pressure influences. Therefore it is not so efficient in maintaining low-pressure conditions in the renal pelvis as when *in situ*.

Pressure in the renal pelvis lessens the circulation through the kidney.

Sudden increase in pressure in the renal pelvis shows more pronounced checking of the circulation than pressure of the same degree when *gradually* exerted.

Retardation of renal circulation by pressure exerted in the renal pelvis tends to be compensated for.

Ureteral peristalsis influences renal circulation and *vice versa.*

IV. Stimulation of the ureter by moderate pressure induces an increased flow of urine.

Pressure exerted in the renal pelvis diminishes the flow of urine.

A pressure of 67 cm. of urine acting in the renal pelvis causes distinct damage to the kidney, as shown by the presence of blood in the urine, and by the macroscopical appearance of the kidney.

V. There appears to be a ureteral influence in the diuresis caused by drugs which increase the muscular activity and tone of the ureter.

Professor William J. Gies made it possible for me to inaugurate my work on the ureter. Since that time he has never ceased to aid, encourage, and instruct me in research on this and other subjects. Whatever scientific or clinical advances have or may result from my efforts in research are directly dependent upon his interest and assistance.

BIOGRAPHICAL

Daniel Ralph Lucas resided in La Fayette, Indiana, from 1881 to 1898 inclusive. He received a public school education in La Fayette. In 1898 he enlisted in the 160th Regiment, Indiana Volunteer Infantry, in which he served during the war with Spain. He was Captain of the Hospital Corps at Purdue University, 1901-1902, and Major of the 1st Batallion and Ranking Cadet officer there in 1902-1903.

At various times from 1901 to 1904 he held the position of prescription clerk at Hogan and Johnson's, and Bartlett's pharmacies in La Fayette, Indiana, and at Stork's pharmacy in Chicago, Ill.

He has been assistant and subject in the Private Research Laboratory of Dr. C. A. Herter at various times since 1905; also assistant chemist and a subject in an investigation by the U. S. Dept. of Agriculture, of the effects of sodium benzoate in food on human metabolism.

He was University Fellow in Biological Chemistry, Columbia University, 1907- 1908, and is Fellow of the Alumni Association of the College of Physicians and Surgeons, Columbia University (1908-1909.)

He has practiced medicine in New York City since 1907.

DEGREES RECEIVED

From Purdue University—Ph. G., 1901; B.S., 1903.
From Columbia University—M.A., 1906; M.D., 1907.

PUBLICATIONS

Studies of the peristalsis of the ureter of the dog by the graphic method. *American Journal of Physiology*, 1906, xvii, p. 392.

Clinical aspects of recent developments in the physiology and pharmacology of the ureter. *New York Medical Journal*, 1907 (August 10).

Pharmacological studies of magnesium salts. VI. (With S. J. Meltzer). *The Journal of Experimental Medicine*, 1907, iii, p. 298.

Physiological and pharmacological studies of the ureter. III. *American Journal of Physiology*, 1908, xxii, p. 245.